L Number	Hits	Search Text	DB	Time stamp
1	10	kidney$10 ADJ specific ADJ promoter	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/02/23 22:57
8	43	sun NEAR tUNG$5	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/02/23 22:58
15	74	uromodulin	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/02/23 23:01
22	98	kidney ADJ specific	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/02/23 23:01
29	3	(kidney ADJ specific) and uromodulin	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/02/23 23:01
36	46	uromodulin and kidney	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/02/23 23:01
43	30	(uromodulin and kidney) AND TRANSGENIC	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/02/23 23:02
-	11260	sun.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/04/23 16:40
-	116	sun.in. and kidney$15	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/04/23 16:40
-	11	(sun.in. and kidney$15) and urine	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/04/23 17:48
-	4	(kidney ADJ specific) and (apical or basolateral)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/04/23 17:15
-	6	XUE-RU	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/04/23 17:49

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(FILE 'HOME' ENTERED AT 22:40:01 ON 23 FEB 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 22:40:11 ON 23 FEB 2003

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L1           18 S KIDNEY SPECIFIC PROMOTER
L2           10 DUP REM L1 (8 DUPLICATES REMOVED)
L3           18 SORT L1 PY
L4            1 S L3 AND URINE
L5           53 S (UROMODULIN OR UROPLAKIN) (L) PROMOTER
L6           24 DUP REM L5 (29 DUPLICATES REMOVED)
L7            9 S L6 AND URINE
L8            9 SORT L7 PY
L9           16 S L6 AND TRANSGENIC
                E SUN TUNG?/AU
L10         122 S E2
L11          53 S L5
L12         163 S L5 OR L10
L13         126 DUP REM L12 (37 DUPLICATES REMOVED)
L14          17 S L10 AND TRANSGENIC
L15          14 DUP REM L14 (3 DUPLICATES REMOVED)
L16          14 SORT L15 PY
```

=> d an ti so au ab L9 9

L9 ANSWER 9 OF 16 MEDLINE
AN 95148601 MEDLINE
TI A tissue-specific promoter that can drive a foreign gene to express in the suprabasal urothelial cells of **transgenic** mice.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Jan 31) 92 (3) 679-83.
Journal code: 7505876. ISSN: 0027-8424.
AU Lin J H; Zhao H; Sun T T
AB **Uroplakins** are a group of integral membrane proteins that are synthesized as the major differentiation products of urothelium. The luminal portions of these proteins form 12-nm protein particles arranged in a two-dimensional crystalline array. The expression of **uroplakin** genes is bladder specific and differentiation dependent; little is known, however, about their molecular regulation. Here we describe the cloning of mouse **uroplakin** II gene and demonstrate, in **transgenic** mouse experiments, that a 3.6-kb 5'-flanking sequence of this gene can drive a bacterial lacZ (reporter) gene to express in the suprabasal cell layers of the urothelium. The transgene was not expressed in any tested (nonurothelial) epithelial and other tissues (except hypothalamus). These results suggest that most of the cis elements that confer the bladder-specific and differentiation-dependent expression of mouse **uroplakin** II gene must reside in the 3.6-kb sequence. The availability of a **promoter** capable of delivering a foreign molecule to the differentiated cell layers of bladder epithelium opens avenues for studying normal and pathological urothelial differentiation in **transgenic** mice.

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(FILE 'HOME' ENTERED AT 22:40:01 ON 23 FEB 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 22:40:11 ON 23 FEB 2003

L1 18 S KIDNEY SPECIFIC PROMOTER
L2 10 DUP REM L1 (8 DUPLICATES REMOVED)
L3 18 SORT L1 PY
L4 1 S L3 AND URINE
L5 53 S (UROMODULIN OR UROPLAKIN) (L) PROMOTER
L6 24 DUP REM L5 (29 DUPLICATES REMOVED)
L7 9 S L6 AND URINE
L8 9 SORT L7 PY

=> d an ti so au ab pi l8 1-9

L8 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 1997:105228 CAPLUS
DN 126:114187
TI Expression of foreign genes in the bladder epithelium and recovery of the gene product in the **urine**
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
IN Sun, Tung-Tien
AB A method for the directing expression of biol. active mols. in the urothelium via use of urothelial-specific **promoters** and a method for producing transgenic animals resulting in the synthesis of biol. active mols. that are secreted into their **urine** for subsequent recovery are provided. Specifically, the **promoter** region of the mouse **uroplakin** II gene is characterized for this use. The **promoter** drives suprabasal cell-specific expression of a reporter gene in transgenic mice. The development of mice secreting human growth hormone into the **urine** at concns. of 400-500 ng/mL is reported. The blood concn. of the hormone was <5 ng/mL.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9639494	A1	19961212	WO 1996-US8233	19960531
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5824543	A	19981020	US 1995-464961	19950605
CA 2221453	AA	19961212	CA 1996-2221453	19960531
AU 9659615	A1	19961224	AU 1996-59615	19960531
EP 837931	A1	19980429	EP 1996-916890	19960531
EP 837931	B1	20020821		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 222601	E	20020915	AT 1996-916890	19960531

L8 ANSWER 2 OF 9 MEDLINE
AN 1998108859 MEDLINE
TI The bladder as a bioreactor: urothelium production and secretion of growth hormone into **urine**.
SO NATURE BIOTECHNOLOGY, (1998 Jan) 16 (1) 75-9.
Journal code: 9604648. ISSN: 1087-0156.
AU Kerr D E; Liang F; Bondioli K R; Zhao H; Kreibich G; Wall R J; Sun T T
AB **Uroplakin** genes are expressed in a bladder-specific and differentiation-dependent fashion. Using a 3.6-kb **promoter** of mouse **uroplakin** II gene, we have generated transgenic mice that express human growth hormone (hGH) in their bladder epithelium, resulting in its secretion into the **urine** at 100-500 ng/ml. The levels of **urine** hGH concentration remain constant for longer than 8 months. hGH is present as aggregates mostly in the **uroplakin**-delivering cytoplasmic vesicles that are targeted to fuse with the apical surface. Using the bladder as a bioreactor offers unique advantages, including the utility of all animals throughout their lives. Using **urine**, which contains little protein and lipid, as a starting material facilitates recombinant protein purification.

L8 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS

AN 1999:794266 CAPLUS
DN 132:31766
TI Expression vectors using urothelium-specific promoters for secretion of proteins into the **urine**
SO U.S., 13 pp., Cont.-in-part of U. S. 5,824,543.
CODEN: USXXAM
IN Sun, Tung-tien
AB A method of manufg. proteins in a mammalian host and recovering them from the **urine** is described. The method uses secretory expression vectors that are driven by a urothelium-specific **promoter**. This leads to secretion of the gene product into the **urine** from where it can be recovered. Specifically, **promoters** of genes for **uroplakins**, the proteins of the asym. unit membrane are used to drive expression of foreign genes. Methods of isolating biol. active mols. from **urine** of animals transfected with this vector and transgenic animals contg. this vector are also provided. **Urine** may be a preferable for the accumulation of proteins with poor soly. because of its high osmolality and the presence of urea, a chaotropic denaturant. The construction of a transgenic mouse carrying the lacZ gene under control of the **promoter** of the mouse **uroplakin** II gene is described. The mouse **uroplakin** II gene had been cloned by probing with the cattle **uroplakin** II gene.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6001646	A	19991214	US 1997-907800	19970808
	US 5824543	A	19981020	US 1995-464961	19950605
	CA 2221453	AA	19961212	CA 1996-2221453	19960531
	US 6339183	B1	20020115	US 1997-969315	19971113
	US 6323390	B1	20011127	US 1998-83541	19980522

L8 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 1999:614110 CAPLUS
DN 131:253338
TI Production of biofilaments such as spider silk in transgenic animals using milk or **urine**-specific promoters
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
IN Karatzas, Costas N.; Turner, Jeffrey D.; Karatzas, Anthoula-Lazaris
AB Disclosed is a method for the recombinant prodn. of biofilaments, such as spider silk or insect fibroins, using transgenic animals which secrete the biofilaments in their milk and/or **urine**, and transgenic cells which secrete the biofilaments into culture media. Such a method is useful for producing large quantities of biofilament material. Also disclosed is a nucleic acid mol. for generating such transgenic animals. Thus, a **promoter** specific for milk-producing cells (goat .beta.-casein gene or murine whey acidic protein gene) or specific for **urine**-producing cells (**uroplakin** II gene) is used to express nucleic acids encoding portions of dragline silk (the Nephila clavipes [golden orb weaver] spidroin 1 and 2, or Araneus diadematus ADF-3). The mammary epithelial or uroepithelial cell lines are transfected with such biofilament-encoding constructs and shown to secrete the spider silk proteins.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9947661	A2	19990923	WO 1999-IB763	19990312
	WO 9947661	A3	20000106		
	W: AU, BR, CA, CN, JP, NZ, SG, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 2001042255	A1	20011115	US 1998-40518	19980317
	CA 2323570	AA	19990923	CA 1999-2323570	19990312
	AU 9931650	A1	19991011	AU 1999-31650	19990312
	EP 1064367	A2	20010103	EP 1999-913549	19990312
	R: BE, DE, FR, GB, NL, FI				
	JP 2002506642	T2	20020305	JP 2000-536844	19990312

L8 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2000:351690 CAPLUS
DN 133:13401
TI Transgenic animals as bioreactors for production of protein in

urine by kidney-specific expression using the **uromodulin** gene **promoter**

SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2

IN Wu, Xue-Ru; Sun, Tung-Tien

AB The invention relates to recombinant DNA constructs, a method for producing a recombinant biol. active protein in vivo in the **urine** of a non-human mammal using a kidney-specific **promoter**, such as the **uromodulin promoter**, and the transgenic non-human mammals that serve as **urine**-based bioreactors for protein prodn. The recombinant DNA construct may also contain a secretion signal sequence operably linked to the heterologous gene. The method for producing a recombinant biol. active protein in vivo in the **urine** of a non-human mammal comprises the steps of introducing the recombinant DNA construct into a fertilized embryo to produce a transgenic non-human mammals expressing and secreting the protein in the **urine**, and collecting the **urine** to recover the protein. The **uromodulin promoter** is preferably of mouse, cattle, or rat, and the transgenic non-human mammal is goat, cow, sheep, pig, or horse. The nucleotide sequences of the mouse and goat **uromodulin** gene **promoter** region were obtained. Recombinant prodn. of human growth hormone in the **urine** of transgenic mouse using the **uromodulin promoter** is described. (no data).

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000029608	A1	20000525	WO 1999-US26870	19991112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1135518	A1	20010926	EP 1999-958952	19991112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

L8 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2000:191195 CAPLUS
DN 132:247143
TI Expression of recombinant proteins in the **urine** of transgenic animals
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
IN Karatzas, Costas N.
AB The invention provides methods which generate a recombinant polypeptide that is secreted into the **urine** of a transgenic animal. The expression of the provided polypeptide is driven by the **uromodulin** gene **promoter** or other **promoters** from genes whose products are specifically expressed in the kidney. The generation of recombinant proteins utilizing an animal as a bioreactor has the advantage of producing a recombinant protein that is likely properly folded.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000015772	A2	20000323	WO 1999-IB1609	19990916
WO 2000015772	A3	20000720		
W: AU, BR, CA, HU, JP, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2343104	AA	20000323	CA 1999-2343104	19990916
AU 9957553	A1	20000403	AU 1999-57553	19990916
EP 1112353	A2	20010704	EP 1999-944741	19990916
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002525047	T2	20020813	JP 2000-570299	19990916

L8 ANSWER 7 OF 9 MEDLINE
AN 2002016628 MEDLINE

TI Expression of recombinant human granulocyte macrophage-colony stimulating factor (hGM-CSF) in mouse **urine**.
SO TRANSGENIC RESEARCH, (2001 Jun) 10 (3) 193-200.
Journal code: 9209120. ISSN: 0962-8819.
AU Ryoo Z Y; Kim M O; Kim K E; Bahk Y Y; Lee J W; Park S H; Kim J H; Byun S J; Hwang H Y; Youn J; Kim T Y
AB We have generated transgenic mice expressing human granulocyte macrophage-colony stimulating factor (hGM-CSF) in **urine**. In particular, the expression plasmid DNA containing mouse **uroplakin** II **promoter** was used to direct uroepithelium-specific transcription of transgene. In this study, hGM-CSF transcript was detected only in bladder uroepithelium as determined by northern blot analysis. Furthermore, hGM-CSF protein was detected in the suprabasal layer of the uroepithelium and ureter by immunohistochemistry. The hGM-CSF was secreted into **urine** at high level (up to 180 ng/ml), and enhanced proliferation of hGM-CSF-dependent human acute monocyte leukemic cells, suggesting that transgenic **urine**-derived hGM-CSF was bioactive. This is the first case of demonstrating biological activity of a cytokine produced in the **urine** of a transgenic animal. Our results demonstrate that bladder can be used as a bioreactor to produce biologically important substances. In addition, it suggests a potential application of bladder expression system to livestock for high-yield production of pharmaceuticals.

L8 ANSWER 8 OF 9 MEDLINE
AN 2002452258 IN-PROCESS
TI The use of the **uromodulin promoter** to target production of recombinant proteins into **urine** of transgenic animals.
SO TRANSGENIC RESEARCH, (2002 Aug) 11 (4) 425-35.
Journal code: 9209120. ISSN: 0962-8819.
AU Zbikowska Halina M; Soukhareva Nadia; Behnam Reza; Chang Rosemary; Drews Roman; Lubon Henryk; Hammond David; Soukharev Serguei
AB A **uromodulin promoter** has been isolated, sequenced, and used to generate two sets of transgenic mice for expression of the lacZ marker gene and for production of the human recombinant erythropoietin (rhEPO) in **urine**. We demonstrated that the 5.6-kb fragment of the **uromodulin** gene containing the 3.7-kb **promoter** area and, both the first exon and part of the second exon, were sufficient to provide kidney-specific expression of the lacZ gene. Histological analysis of the lacZ expression pattern revealed beta-galactosidase activity specifically in the thick limb of Henle's loop. However, due to random integration of the transgene, ectopic expression was detected in some transgenic lines. Analysis of the EPO-transgenic mice showed that rhEPO was secreted into the **urine** of founder mice (up to 6 ng/ml). We were able to breed and analyze only two sublines with a very low expression level of rhEPO (up to 260 pg/ml). All of our transgenic mice expressing rhEPO in **urine** developed disease symptoms similar to polycythemia in humans. These included a considerable increase in red blood cell counts, hemoglobin concentration, and hematocrit concomitant with severe thrombocytopenia, all of which were detected in the rhEPO-expressing mice. Although our model did not prove to be beneficial for commercial production of rhEPO, we concluded that the **uromodulin promoter** could be useful for expression of other important therapeutic proteins into the **urine** of transgenic animals.

L8 ANSWER 9 OF 9 MEDLINE
AN 2002361590 MEDLINE
TI **Uromodulin promoter** directs high-level expression of biologically active human alpha1-antitrypsin into mouse **urine**.
SO BIOCHEMICAL JOURNAL, (2002 Jul 1) 365 (Pt 1) 7-11.
Journal code: 2984726R. ISSN: 0264-6021.
AU Zbikowska Halina M; Soukhareva Nadia; Behnam Reza; Lubon Henryk; Hammond David; Soukharev Serguei
AB We have recently shown that the regulatory sequence of the **uromodulin** gene, containing the 3.7 kb **promoter**, exon 1 and a part of exon 2, provided for kidney-specific expression of the reporter lacZ gene in transgenic mice [Zbikowska, Soukhareva, Behnam, Chang, Drews, Lubon, Hammond and Soukharev (2002) Transgenic Res., in the

press]. In the present study, we generated transgenic mice harbouring the regulatory sequence of the **uromodulin** gene to direct the expression of human alpha1-antitrypsin (alpha1AT) into **urine**. Of the 13 founder mice that tested positive by PCR, seven showed the presence of the human protein in their **urine**. The concentration of the recombinant human (rh) alpha1AT in the **urine**, estimated by using ELISA, ranged from 0.5 to 14 microg/ml in the F(0)-generation mice, and reached up to 65 microg/ml in the F1 generation. The transgenically produced rh alpha1AT was found to be N-glycosylated and biologically active. The N-terminal sequence analysis confirmed the identity of the human protein and revealed that the recombinant alpha1AT was correctly processed with the signal peptide cleaved off. Our results demonstrate for the first time that the **uromodulin** regulatory sequence provides a very attractive option for the potential large-scale production of functional therapeutic proteins in livestock.

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     (FILE 'HOME' ENTERED AT 22:40:01 ON 23 FEB 2003)

     FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED
     AT 22:40:11 ON 23 FEB 2003
L1            18 S KIDNEY SPECIFIC PROMOTER
L2            10 DUP REM L1 (8 DUPLICATES REMOVED)
L3            18 SORT L1 PY
L4             1 S L3 AND URINE
L5            53 S (UROMODULIN OR UROPLAKIN) (L) PROMOTER
L6            24 DUP REM L5 (29 DUPLICATES REMOVED)
L7             9 S L6 AND URINE
L8             9 SORT L7 PY
L9            16 S L6 AND TRANSGENIC

=> d an ti so au ab 19 9

L9   ANSWER 9 OF 16     MEDLINE
AN   95148601     MEDLINE
TI   A tissue-specific promoter that can drive a foreign gene to express in the
     suprabasal urothelial cells of transgenic mice.
SO   PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF
     AMERICA, (1995 Jan 31) 92 (3) 679-83.
     Journal code: 7505876. ISSN: 0027-8424.
AU   Lin J H; Zhao H; Sun T T
AB   Uroplakins are a group of integral membrane proteins that are
     synthesized as the major differentiation products of urothelium. The
     luminal portions of these proteins form 12-nm protein particles arranged
     in a two-dimensional crystalline array. The expression of
     uroplakin genes is bladder specific and differentiation dependent;
     little is known, however, about their molecular regulation. Here we
     describe the cloning of mouse uroplakin II gene and demonstrate,
     in transgenic mouse experiments, that a 3.6-kb 5'-flanking
     sequence of this gene can drive a bacterial lacZ (reporter) gene to
     express in the suprabasal cell layers of the urothelium. The transgene was
     not expressed in any tested (nonurothelial) epithelial and other tissues
     (except hypothalamus). These results suggest that most of the cis elements
     that confer the bladder-specific and differentiation-dependent expression
     of mouse uroplakin II gene must reside in the 3.6-kb sequence.
     The availability of a promoter capable of delivering a foreign
     molecule to the differentiated cell layers of bladder epithelium opens
     avenues for studying normal and pathological urothelial differentiation in
     transgenic mice.
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